Information

Clinical Ecology—A Critical Appraisal

In 1981 the California Medical Association (CMA) adopted the position that clinical ecology does not constitute a valid medical discipline and that scientific and clinical evidence to support the diagnosis of "environmental illness" and "cerebral allergy" or the concept of massive environmental allergy is lacking. As a result of requests from clinical ecologists for an opportunity to present to CMA evidence justifying their diagnostic and treatment methods, the chair of the CMA Scientific Board, Allen W. Mathies, Jr, MD, appointed a task force in 1984 to review clinical ecology. The task force conducted an extensive literature review and held a hearing.

Clinical ecology is based on two main hypotheses: first, that the total load of low-dose environmental stressors is important in the induction of illness; and, second, that changes in the frequency of and intervals between exposures to specific substances can mask the clinical manifestations of or alter the degree of sensitivity to those substances. Treatment methods used by clinical ecologists include avoidance, symptom-neutralizing doses of diluted extract of the offending agents, rotation diets and an ecologically sound workplace and home.

The task force recognizes that certain environmental chemicals and allergens produce well-defined syndromes in humans and that some patients suffer from illnesses that are not readily diagnosed and for which only supportive therapy exists. The conclusions of the task force are

- *There is no convincing evidence that supports the hypotheses on which clinical ecology is based.*
- *Clinical ecologists have not identified specific, recognizable diseases caused by exposure to low level-environmental stressors.*
- *Methods to diagnose and treat such undefined conditions have not been shown to be effective.*
- *The practice of clinical ecology can be considered experimental only when its practitioners adhere to scientifically sound research protocols and inform their patients about the experimental nature of their practice.*

(California Medical Association Scientific Board Task Force on Clinical Ecology: Clinical ecology—A critical appraisal [Information]. West J Med 1986 Feb; 144:239-245)

The practice of clinical ecology has been proposed as an alternative approach to the practice of environmental medicine. Practitioners of clinical ecology maintain that a broad range of common physical and psychological disorders can be triggered in susceptible persons by ongoing low-level exposure to foods, environmental chemicals and natural inhalants. Because the medical community has been reluctant to accept clinical ecology concepts, many practitioners of clinical ecology are redesignating their treatment practices "allergy and environmental medicine."

This paper is the result of deliberations by the California Medical Association (CMA) Scientific Board's Task Force to Evaluate Clinical Ecology. In 1981 the CMA Scientific Board reviewed clinical ecology in cooperation with the CMA Scientific Advisory Panels on Allergy, Internal Medicine, Pediatrics and Preventive Medicine & Public Health and the Committee on Environmental Health. The conclusions of this review were that

- clinical ecology does not constitute a valid medical discipline;

A report of the Task Force on Clinical Ecology of the Scientific Board of the California Medical Association. W. C. Wiederholt, MD, was Chair of the task force; the other members were Charles E. Becker, MD; Carroll Brodsky, MD; Gideon Letz, MD; Michael Miller, MD; John Peters, MD; Edward Smuckler, MD; Stephen Wasserman, MD; Antony Gualtieri, MD, and Linda Ramsey. Their names and affiliations are given in Appendix A at the end of this article.

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• scientific and clinical evidence to support the diagnosis of "environmental illness" and "cerebral allergy" or the concept of massive environmental allergy is lacking.

Because of repeated requests from some clinical ecologists for an opportunity to present to CMA evidence justifying their diagnostic and treatment methods, the chair of the Scientific Board, Allen W. Mathies, Jr, MD, appointed a task force in August 1984. The charge to the task force was to review pertinent material, to conduct a hearing at which clinical ecology proponents could present their views and to formulate recommendations to the CMA. The task force did not address any political or economic issues but strictly limited itself to a scientific evaluation of the evidence. The three main questions the task force addressed were as follows:

1. Are there certain symptoms or signs that would allow physicians to identify specific diseases or syndromes induced by low-level environmental exposure as defined by clinical ecologists?

2. Do reliable tests exist that provide objective evidence of such diagnoses?

3. Are there proved therapies that are beneficial for patients who have been identified as having symptoms related to environmental exposure?

These questions were addressed by a review of available literature and at a hearing where practitioners of clinical ecology and others presented additional evidence. Before discussing the methodology, results and conclusions of our appraisal, a brief overview of the basic tenets composing current clinical ecology practice is in order.

Overview of Clinical Ecology

Clinical ecology is based on two main hypotheses. First, the total load of low-dose environmental stressors is important in the induction of illness; and, second, changes in the frequency, intensity of and intervals between exposure to a specific substance can mask the clinical manifestations of or alter the degree of sensitivity to that substance. Clinical ecologists focus on psychophysiological, psychiatric and central nervous system syndromes. They believe that these are the results rather than the causes or correlates of sensitivities to environmental agents. Great emphasis is placed on the role of environmental chemicals and foods. The most common triggers of chronic ecologic illness are considered to be frequently ingested or inhaled substances including foods and indoor as well as outdoor air pollutants. Patients frequently are debilitated by their chronic symptoms.

Every system of the body may be affected. Symptoms and signs include depression, irritability, mood swings, inability to concentrate or think clearly, poor memory, fatigue or drowsiness; diarrhea, constipation, cramps, gas pain or bloating; sneezing, nasal congestion, runny nose, asthma, itching eyes and nose, eczema and skin rashes, and a diverse array of other symptoms such as headache, muscle and joint pain, swelling of various parts of the body, urinary frequency or pain, pounding heart, dark circles under the eyes and cold or tingling extremities.

Potential stressors in the workplace, home and external environment include practically everything that modern men and women come into contact with or use. Some of those identified are polluted urban air, diesel exhaust, tobacco smoke, fresh paint or tar, organic solvents and pesticides, new soft plastics, newspaper print, perfumes and colognes, unvented gas appliances, new building material and poorly ventilated new buildings, permanent press and synthetic fabrics, household cleaners, rubbing alcohol, felt-tip pens, cedar-lined closets and tap water. Low doses of substances that alone might be benign may interact additively or synergistically on some common pathways in the body to produce illness. The greatest response to many stressors usually is evoked by the initial exposure after sensitization has been established. If exposure is frequent, however, the body may adapt by progressively dampening its acute response—but low-grade problems persist and are not easily recognized.

In contrast to allergic disorders, which are frequently IgE related and manifest themselves in the skin or in the respiratory system, environmental illnesses may be related to IgE and immune complexes—or other still unknown mechanisms—and may involve all bodily systems. The diagnosis of environmental illness is made by a detailed clinical, dietary and environmental history. Suggestive laboratory evidence includes altered levels of T- and B-cell subsets. A patient's response is tested further by clinical avoidance and challenge tests, by serial dilution titration methods using skin tests, by provocation-neutralization tests and by the cytotoxic test.

The endpoint dilution for a particular stressor is determined with the serial dilution titration method. Optimal dose treatment is then instituted with some fraction or multiple of values of the 0.01-ml endpoint dose with the goal to find the dose that will induce symptom relief for as long as possible between injections. In the provocation-neutralization test, a suspected offending substance is diluted and administered either intradermally or sublingually. The neutralizing dose is the concentration that relieves a patient's symptoms while a higher or lower dose will provoke symptoms. The cytotoxic blood test is based on the assumption that extracts of chemicals and foods to which the patient is sensitive will induce visible damage to the patient's platelets or leukocytes. The mainstays of treatment are avoidance or elimination of stressors in the diet or the environment, rotation diets, optimal dose intradermal treatment, neutralization treatment and an ecologically sound workplace and home. Environmental control units play a prominent diagnostic and treatment role in some centers.

Methodology

Members of the Task Force were chosen for their expertise in internal medicine, toxicology, epidemiology, occupational medicine, allergy, immunology, pathology, neurology and psychiatry. By necessity, the task force concentrated primarily on a thorough and critical review of the pertinent literature. Many references were provided by the petitioners. In addition, an independent search of the literature was conducted and articles were solicited from the American Academy of Environmental Medicine (formerly the Society for Clinical Ecology), the American Academy of Otolaryngic Allergy and the Pan-American Allergy Society. Key articles and books were reviewed by all members of the task force. Other articles requiring specific expertise were reviewed by individual members who then presented their findings to the group.

The task force agreed to accept certain criteria to make the

literature review process as objective as possible. These criteria have been published[1-3] but will be briefly summarized.

To assess *causation* of environmental illness, the following questions were raised:

1. Is there evidence from either experimental studies in humans (such as randomized controlled trials) or epidemiologic studies (such as cohort or case-control studies)?
2. Is the association strong?
3. Is the association consistent from study to study?
4. Is the temporal relationship correct?
5. Is there a dose-response relationship?
6. Does the association make epidemiologic sense?
7. Does the association make biologic sense?
8. Is the association specific?
9. Is the association consistent with a previously proved causal association?

To assess *prognosis* the following questions were asked:

1. Was an inception cohort assembled?
   a. Were patients identified at an early and uniform point in the course of their disease?
   b. Were the diagnostic criteria, disease, severity, co-morbidity and demographic details for inclusion clearly specified?
2. Was a referral pattern described?
3. Was complete follow-up achieved?
4. Were objective outcome criteria developed and used?
5. Was outcome assessment blind?
6. Was adjustment for extraneous prognostic factors carried out?

Diagnostic tests were subjected to the following questions:

1. Was there an independent, "blind" comparison with a "gold standard" of diagnosis?
2. Was the setting for the study and the filter through which study patients passed adequately described?
3. Did the sample include an appropriate spectrum of mild and severe, treated and untreated patients, plus persons with different but commonly confused disorders?
4. Were the methods for carrying out the tests described in sufficient detail to permit their exact replication?
5. Was the reproducibility of the test result (precision) and its interpretation (observer variation) determined?
6. Was the term "normal" defined sensibly? (Gaussian; percentile; risk factor; culturally desirable, diagnostic or therapeutic?)
7. If the test was advocated as part of a cluster or sequence of tests, was its contribution to the overall validity of the cluster or sequence determined?
8. Was the "utility" of the test determined? (Were patients really better off for it?)

Articles dealing with *therapy* were evaluated by asking the following questions:

1. Was the assignment of patients to treatments really random?
   a. Was similarity between groups documented?
   b. Was prognostic stratification used in allocation?
2. Were all clinically relevant outcomes reported?
   a. Were mortality and morbidity reported?
   b. Were deaths from all causes reported?
   c. Were quality of life assessments conducted?
   d. Was outcome assessment blind?
3. Were both statistical and clinical significance considered?
   a. If statistically significant, was the difference clinically important?
   b. Was the study population large enough to show a clinically important difference if it should occur?
4. Were all patients who entered the study accounted for at its conclusion? (Were drop-outs, withdrawals, noncompliers and those who crossed over handled appropriately in the analysis?)

A significant portion of the literature that was made available to the task force consisted of individual case reports, testimonials and newspaper articles. While all materials were thoroughly reviewed, only publications that satisfied at least some of our review criteria were seriously considered.

Hearing

A hearing was conducted by the task force on April 30, 1985. Presenters were selected by the petitioners and the task force. Each presenter was given equal time. Presenters included Drs Fricke, Boyles, Rea, Buttler, Finn, Brostoff, Jewett and Whittington and Mr Levin. Their names, addresses and affiliations are given in Appendix B. The hearing was public and a number of interested persons attended. Because the purpose of the hearing was to gather additional information and to clarify certain unresolved questions, discussion was limited to presenters and task force members.

Some presentations were testimonials and others addressed known environmental pollutants and well-established disease entities not relevant to the charge of the task force. Still others provided some new data, but without the benefit of a detailed analysis of the study design, no judgment can be made at this time. Presenters were invited to send additional written information to the task force after the hearing and several did so.

Discussion of Published and Unpublished Papers

The task force was not charged with and did not conduct an extensive review of established allergic disorders and known or suspected environmental pollutants. Because material addressing these issues was submitted, we did review it but did not include it in our assessment. The task force also reviewed numerous publications that, by their nature, do not lend themselves for critical analysis or do not contain information that would be helpful to illuminate or answer the questions raised. These publications are listed in Appendix C and include books, editorials, position and policy statements, newspaper articles, symptom lists, letters, medical reports, case reports, course outlines, papers or presentations dealing with known or suspected pollutants, political statements, publications dealing with issues of medical quality assurance and legal aspects, review articles, research proposals, instruction papers, manuals and books and articles of unknown source.

The following section will discuss papers reviewed by the task force which either appeared relevant to our inquiry, or which the petitioners offered as evidence documenting the

efficacy of diagnostic and treatment methods in clinical ecology, or which satisfied at least some of our review criteria.

Three papers by Miller were reviewed. The first, a double-blind study of food extract injection therapy,[4] was found to contain statistically inappropriate data analysis. The second paper by the same author[5] is a discussion of the previous paper using the same patient population. Miller's third paper, "Treatment of Active Herpes Virus Infections With Influenza Virus Vaccine,"[6] was not a blinded study nor were the patients randomly assigned. A study by Burr and Merrett,[7] which represents a community survey of food intolerance in Great Britain, reported no association between food intolerance and allergic histories and also found that plasma IgE was lower in women with food intolerance. The study by Gardner and co-workers[8] investigating the role of plant and animal phenols in food allergy simply reported observations of 100 patients without random assignment.

The Society for Clinical Ecology, in a statement submitted to the California Board of Medical Quality Assurance,[9] cited the three papers reviewed below as best demonstrating the validity of the basic hypotheses of clinical ecology.

McGovern and associates[10] published a paper on food and chemical sensitivity describing six allergic patients and six normal controls. There was no definition of the disease entity being diagnosed or treated. Before challenge testing, the normal subjects showed no blood abnormalities, but the patients showed a mean of 3.7 abnormalities among the 15 immunopharmacologic components measured in their plasma. The most common abnormalities noted were depressed levels of epinephrine and IgE and elevated levels of CH-100. That allergic subjects are different immunologically from nonallergic subjects is not surprising. This study did not address the issue of provocation-neutralization or the efficacy of any treatment. Patients were not differentiated from controls and no criteria were given for patient selection and the filtering process. Similar problems were encountered in the study by Rea.

Rea and associates[11] addressed the issue of subcutaneous injection of food extracts in a neutralizing dose to reduce symptoms related to food allergies. From their general patient population the authors selected a subgroup of persons who could be "neutralized." Diagnostic criteria were not specified. Subjects apparently had experienced one of multiple symptoms, many vague and not objectively measureable, after oral food challenge. Subjects, testing technicians and observers were ignorant of the content of each injection until after the response was judged to be positive or negative. The technician knew that one dose was neutralizing and two were placebos. Thus, if the first dose was neutralizing, the technician would know that the next two were placebos, which could influence the judgment of the observing technician. If the injections were truly random, the technician would know what the dose was in 27 cases and not know in 37 cases. Because the technician would know nearly half the time what was being administered, this study cannot be considered a truly blind evaluation. Further, even if this study had no methodological flaws, it is not justifiable to assume that results obtained in a highly selected group of patients are applicable to the general clinical ecology patient population. A study by Boris and co-workers[12] dealt with patients with asthma. The patients were their own controls, with pulmonary function measured in response to an inhalation challenge with antigen before and after injection of the "neutralizing" dose or placebo. The relevance of this study to populations without history of asthma must be seriously questioned. It is unlikely to be relevant to other populations simply defined as "chemically sensitized."

A study by Miller[13] presented information on eight cases treated by alternating neutralizing doses with doses of placebo. The order of the neutralizing dose and placebo was started randomly but then alternated. Presumably the patients did not know what they were receiving and the physician judging the complaints did not know what the patients were receiving. In general, there was a correlation between decreased symptoms and the use of a neutralizing dose. Sometimes administration of the placebo caused the symptoms to return and in three cases it did not. In these three cases in which symptoms did not return while the patient received a placebo, this was referred to as a "holdover" phenomenon. In other words, no matter what the result in these three persons, it could be explained. These eight cases were presented as eight cases in succession. If these were eight cases in succession, if the patients did not know what they were receiving and if the person who judged the symptoms was blinded, this paper does provide some evidence that neutralizing doses can be useful in relieving some symptoms. Nevertheless, since the interpretation by the investigator indicates that regardless of outcome, patients who received the neutralizing dose would improve, this study cannot be accepted as sound evidence.

In a 1983 study conducted by Jewett and Greenberg (D. L. Jewett, MD, and M. R. Greenberg, MD, Department of Orthopedic Surgery, University of California, San Francisco, March 10, 1983) and presented at the April 30 hearing, 18 subjects in 8 different clinical ecology offices were tested under double-blind conditions to determine whether or not food extracts below a so-called neutralizing dose would provoke symptoms. Patients were selected by their treating physicians. Only subjects were entered who, under unblinded conditions, had been shown to have symptoms reliably provoked by injection of food extracts and relieved by neutralizing doses—but who had shown no reaction to injections of saline. In the experimental, double-blinded situation, the ratio of symptoms to injections was identical for both the active and the control injections (27% and 26%, respectively). Therefore, in this study, symptom provocation by intradermal testing of food extracts represents a placebo response.

A. I. Terr, MD, evaluated 50 patients who had been previously diagnosed by 16 different clinical ecologists as having environmental illness.[14] In 41 patients the result of provocation-neutralization testing was used by clinical ecologists to support their diagnosis. All 50 patients received some form of clinical ecologic treatment. Clinical histories and offending chemicals were so heterogeneous that no patterns of symptomatology emerged to define a disease, syndrome or nosologic entity. In only 2 of the 50 patients was there diminution in number and severity of symptoms as reported by the patient. In spite of treatment, 26 reported no change in their symptoms while 22 worsened. This group of patients does not represent a random sample but the observations suggest that a number of patients with environmental illnesses diagnosed by

clinical ecologists do not benefit or are even made worse while under treatment by a clinical ecologist.

Conclusions

The task force collected material as for any subject review and included all information supplied by individual clinical ecologists and by their professional organizations. There was extensive description of the basic hypotheses of clinical ecology, and an ample and varied collection of anecdotal reports and individual patient testimonials. In contrast, there was a surprising paucity of published studies to prove or disprove clinical ecology hypotheses. Critical analyses of patients and cohorts, detailed data collection, validation and confirming laboratory assays were not provided.

No convincing evidence was found that patients treated by clinical ecologists have unique, recognizable syndromes, that the diagnostic tests employed are efficacious and reliable or that the treatments used are effective. Even though clinical ecology has existed for approximately 50 years, only a few studies have been conducted that are scientifically sound. Most have such serious methodological flaws as to make their conclusions unacceptable. Those few studies that used scientifically sound methods have provided evidence that the effectiveness of certain treatment methods used by clinical ecologists is based principally on placebo response.

Undoubtedly, some patients suffer from illnesses that cannot be readily diagnosed and for which only supportive treatments exist. It may even be true that some or all of the hypotheses and treatments proposed by clinical ecologists are valid but we found no evidence to support them. These hypotheses and treatments should be subjected to modern, scientific methods of evaluation. We think that this can be done provided genuine interest exists.

The task force is concerned that unproved diagnostic tests are being widely used by clinical ecologists in what may be incorrect or inappropriate applications. Decisions made on the basis of these tests can lead to misdiagnosis, resulting in patients being denied other supportive treatments and becoming psychologically dependent, believing themselves seriously and chronically impaired. This possibility underscores the need for more adequate scientific studies to prove or disprove the value of clinical ecology tests and treatments. To consider the current practice of clinical ecology experimental is misleading, however. It can only be considered experimental when its practitioners adhere to scientifically sound research protocols and inform their patients about the investigative nature of their practice.

APPENDIX A

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APPENDIX B

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APPENDIX C

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